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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,546	12/04/2003	Paolo Chiesi	245855US0CIP	5501

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
11/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/726,546	CHIESI ET AL.	
	Examiner	Art Unit	
	JAGADISHWAR R. SAMALA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-48 and 54-60* is/are pending in the application.

4a) Of the above claim(s) *35-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-34 and 54-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Acknowledgement is made of amendment filed on 08/05/2008. Upon entering the amendment, claim 56-60 are newly added. Accordingly, claims 8-34 and 54-60 are pending and are presented for examination.

Response to Arguments

2. Applicant's arguments filed on 08/05/2008 with respect to claims under U.S.C. 35 103(a) have been fully considered but they are not persuasive. The 103 (a) rejection of Nishimura et al (US 3,961,041) and Chiesi (US 4,826,875) in view of Hagemann et al (US 5,211,957) or Wehling et al (US 5,503,846) is maintained and **FINAL**.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 8, 12, 17-18, 22 and 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishimura et al (US 3,961,041).

Nishimura discloses a pharmaceutical composition comprising effervescent-enteric coated tablet comprising L-DOPA or a derivative (levedopa methyl ester or pharmaceutically acceptable acid addition salt) capable of enzymatically cleaving and reverting to L-DOPA in vivo (see abstract and claim 1).

Nishimura also discloses effervescent acid-base couples as agents that act as sources of carbon dioxide are pharmaceutically acceptable acids such as tartaric acid, citric acid, citric anhydride, phthalic acid and sodium bicarbonate or any equivalent thereof. Additional exemplary carbon dioxide releasing agents can also be found in "Remington's Pharmaceutical Sciences", pages 802,803 and 1462 (see col. 3 lines 21-35).

Nishimura further discloses that the enteric film dissolves rapidly in the upper part of the small intestine and upon contact of the effervescent-enteric coated tablet with the intestinal juice; a large amount of L-DOPA or any suitable derivative thereof will be released therefrom, whereby it will be dissolved in the intestinal juice all at once. The dissolved L-DOPA is absorbed as it is from the optimum absorption site and conversion of L-DOPA into dopamine is quite remarkably inhibited. As a result, the maximum blood-concentration of unchanged L-DOPA, which is obtainable by using such preparation, is three to seven times higher than that reached when administering L-DOPA via a conventional enteric-coated tablet.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a composition comprising levodopa methyl ester and an acid-base couple, wherein composition is free of coating, because both Applicant and Nishimura discloses composition comprising such components.

Applicant argues that there is nothing in Nishimura et al. which would even remotely suggest preparing a formulation which exhibits such a short maximum concentration time. The Examiner finds that this argument is unpersuasive, because it is

known that it takes 20-60 minutes to digest food particles accordingly to (Elle magazine, Turkish edition, October 2006, page 3). Nishimura teaches that the enteric film dissolves rapidly in the upper part of the small intestine, i.e., the optimum absorption site therein. Upon contact of the effervescent-enteric coated preparation with the intestinal juice, a large amount of active drug will be released therefrom and is absorbed. Since Nishimura teaches same drug and an acid-base couple as an effervescent agent, when administered orally will be capable of providing said maximum plasma concentration as claimed.

3. Claims 8-34 and 54-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi (US 4,826,875) in view of Hagemann et al. (US 5, 211,957) or Wehling et al. (US 5,503,846).

Chiesi discloses a pharmaceutical composition for oral administration, in the form of capsules or tablets as an immediate release of active ingredient. And also discloses compositions for oral, buccal, sublingual or rectal administration containing active ingredient such as levodopa methyl ester in an unit dose ranging from 100 to 300 mg in combination with carbidopa in a ration ranging from 4:1 to 10:1 (see abstract and col.3 lines 30-35). Chiesi further discloses the buccal delivery of LDME administration by small tablets which adhere to the surface of the oral mucosa releasing drug amounts constant in time, assuring steady plasmatic levels and consequently avoiding fluctuating clinical responses (see col. 2 lines 55-60).

Chiesi fails to disclose pharmaceutical composition wherein additional acid-base couples such as sodium glycine carbonate and fumaric acid capable of reacting rapidly with base, an effervescent action occurs as the carbon dioxide gas is desorbed from the inorganic oxide material. However the use of sodium glycine carbonate and fumaric acid as an effervescent acid-base couple, suitable for dissolving in water or an aqueous solution is well known in the art as shown by Hagemann or Wehling.

Hagemann discloses a solid, rapidly disintegrating effervescent tablet for producing an aqueous suspension of drug for per oral administration. And dosage form contains diclofenac as drug and the effervescent tablets disintegrates in water, accompanied by evolution of carbon dioxide gas, within one minute to form a slightly turbid aqueous potable, neutral or even pleasant tasting suspension of the active drug (see abstract and col. 2 lines 60-65). And also discloses effervescent tablets containing an agent which acts as a source of carbon dioxide are pharmaceutically acceptable mono- and dibasic salts of carbonic acid, for e.g. alkali metal carbonates or alkali bicarbonates such as sodium or potassium carbonate, calcium or magnesium carbonate, sodium glycine carbonate and pharmaceutically acceptable acids for e.g. organic acids such as tartaric acid, malic acid, fumaric acid, adipic acid, succunic acid, ascorbic acid or maleic acid and the like (see col. 5 lines 5-24).

Wehling discloses a pharmaceutical composition of rapidly dissolvable effervescent tablets comprising drug (such as antacids, analgesics, antibiotics, antihistamines, antispasmodics and the like) and the effervescent couple includes a solid core of an edible acid and a coating of an edible base (see abstract and col. 5

lines 39-50). And effervescent couple includes compounds which evolve carbon dioxide gas such as citric acid, tartaric acid, malic acid, fumaric acid, adipic acid and succinic acid, etc, and carbonate sources include dry solid carbonate and bicarbonate salts such as sodium or potassium carbonate, sodium or potassium bicarbonate, sodium glycine carbonate, lysine carbonate and the like (see col. 7 lines 5-25).

It would have been obvious to one of ordinary skill in the art to modify the pharmaceutical composition disclosed by Chiesi to include sodium glycine carbonate-fumaric acid as an effervescent acid-base couple as an effervescent agent as a means of administering solubilized therapeutic agents. Various effervescent compositions are known which have exothermic heats of solution. A number of these are listed in Lange's

Handbook of Chemistry, 1lth edition, in table 9-6 (page 9-107). The greater the value of the heat of solution, the more heat is liberated per gram-mole of the substance. In view of Hagemann or Wehling, motivation would come from rapidly disintegrating dosage forms in the form of effervescent tablets for producing an aqueous suspension which is suitable for per oral administration.

When these references are taken together, one would have been motivated to extend Hagemann or Wehling's teaching to include the sodium glycine carbonate-fumaric acid as an effervescent acid-base couple in the pharmaceutical composition disclosed by Chiesi to maximize therapeutic efficacy. As suggested by cited references, one would have reasonably expected successful addition of effervescent acid-base couple (such as sodium glycine carbonate-fumaric acid) because the effervescent acid-base couple taught by Hagemann or Wehling, while having a similar therapeutic

effectiveness, provides an additional ability to achieve not only the desire to stability and acid neutralization capacity, but also the size, shape and hardness necessary to survive normal packaging and handling while at the same time providing a tablet which is neither intimidating to the consumer or too slow in disintegration of the dosage form to be generally useful.

One would have been motivated to do so, with reasonable expectation of success because it is always desirable to have extended therapeutic modalities to improve patient's compliance by enhancing patient satisfaction and increasing the selection option. The techniques and skills required for making such substitution is conventional knowledge or well within the skills of ordinary artisan as evidenced by these references cited.

The daily dosages are well suggested and minor variations (concentration and drug release profile) can be easily titrated and obtained in order to determine best outcomes, and it is considered to be routine practice especially having dosage suggestions by Chiesi and Hagemann work. Said difference would not render the claimed invention patentably distinct, it is obvious because the modification is well within the skilled level of the artisan and considered to be a routine optimization commonly practiced in the art, as evidenced by cited references.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities, and pertinent to the problem which applicant concerns about. MPEP 2141.01 (a).

Applicant argues that Chiesi composition does not contain an effervescent couple and also, there is nothing in either Hagemann or Wehling which would lead to the actual combination of glycine sodium carbonate and fumaric acid.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking individually where the rejections are based on combination of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed.Cir.1986).

In this case, the Chiesi patent is relied upon to show that it is known in the art to use a pharmaceutical composition for oral administration comprising unit dosage of levodopa methyl ester alone or combined with other active agent such as carbidopa. In this case, applicant is correct that Chiesi does not teach effervescent couple and this is why the rejection is not one of anticipation. But the Hagemann or Wehling's patent were relied upon to shows in the art an acid-base effervescent couple namely glycine sodium carbonate and fumaric acid in pharmaceutical composition. Further Chiesi teaches that the rapid attainment of high concentrations of levodopa in the systemic circulations after LDME administration produces a very early onset of the therapeutic effect, which appears at 20-30 minites about from the administration of the composition. Thus Chiesi in combination with Hagemann or Wehling would obviously provide a pharmaceutical composition can be formulated in the conventional manner with releasing drug amounts constant in time, assuring steady plasmatic levels and consequently avoiding fluctuating clinical responses.

Conclusion

1. No claims are allowed at this time.

2. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR R. SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr